

One- and two-particle microrheology

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We study the dynamics of rigid spheres embedded in viscoelastic media and address two questions of importance to microrheology. First we calculate the complete response to an external force of a single bead in a homogeneous elastic network viscously coupled to an incompressible fluid. From this response function we find the frequency range where the standard assumptions of microrheology are valid. Second we study fluctuations when embedded spheres perturb the media around them and show that mutual fluctuations of two separated spheres provide a more accurate determination of the complex shear modulus than do the fluctuations of a single sphere.

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Microrheology is an important experimental probe of the viscoelastic properties of soft materials [1]. Unlike more traditional macrorheology, in which a sample is subjected to an externally imposed uniform shear strain, microrheology relies on the Brownian fluctuations of the micron-sized beads dispersed in the sample to assess the viscoelastic response function (complex shear modulus), $G(\omega)$. The principal advantages of this technique are that it can be used for the detailed study of materials that cannot be produced in bulk quantities and that it can be used to probe the local properties of rheologically inhomogeneous materials. Because of these two strengths, microrheology promises to open a new window on cellular biology by facilitating the study of the rheological properties of intra-cellular structures in living cells. In addition, this technique is currently being used to study various soft biomaterials [2].

In a typical microrheology experiment, the time-dependent position correlation function of individual probe particles is measured either by light scattering [2] or by direct real-space imaging [3]. This correlation function provides a complete description (via the Fluctuation–Dissipation Theorem) of the frequency-dependent response of the probe particles to an external force. If inertial effects are ignored, the rheological properties of a Newtonian fluid are completely determined by a single quantity, its viscosity η . The displacement of a spherical particle, $\mathbf{u}(\omega)$, of radius a in response to a force $\mathbf{f}(\omega)$ at frequency ω in such a fluid is given by the standard Stokes–Einstein relation:

$$u(\omega) = \frac{f(\omega)}{6\pi a G(\omega)}, \quad (1)$$

where $G(\omega) = -i\omega\eta$ is the complex shear modulus. A natural hypothesis [1] is that this relation can be generalized to rheologically complex materials in which $G(\omega)$, the complex shear modulus has both storage (real) and loss (imaginary) components. We will refer to this extension of Eq. (1) as the Generalized Stokes–Einstein relation (GSER).

In this Letter we address two basic questions regarding the interpretation of microrheological data: (1) In a ho-

homogeneous viscoelastic medium does the GSER provide the correct response function to an applied force? and, (2) if the introduction of the probe particles perturbs the local rheological properties of the medium, how does one extract the unperturbed, bulk rheological properties from the data? Recent experiments suggest that, at least in certain systems, a discrepancy exists between the macro- and microrheological measurement of the shear modulus [3] making this question one of current interest.

To address the first of these questions, we use a model viscoelastic medium consisting of an elastic network that is viscously coupled to a fluid in which the network is embedded [4,2]. In the second half of this letter, we approach the problem of rheological inhomogeneities and explicitly show that *inter-particle* position correlations are insensitive to the local particle environment, and therefore, provide a more reliable probe of the properties of the bulk material than do single particle fluctuations as proposed in reference [3].

Our model viscoelastic medium consists of an elastic network, characterized by a displacement variable \mathbf{u} , that is viscously coupled via a friction coefficient Γ to an incompressible Newtonian fluid characterized by a velocity field \mathbf{v} . In the absence of viscous coupling, \mathbf{u} obeys the standard equation for an isotropic, elastic, compressible medium with Lamé coefficients λ , μ , and \mathbf{v} obeys the incompressible Navier–Stokes equation with viscosity η . With friction included, the equations for \mathbf{u} and \mathbf{v} [4] are

$$\rho\ddot{\mathbf{u}} - \mu\nabla^2\mathbf{u} - (\lambda + \mu)\nabla(\nabla \cdot \mathbf{u}) = -\Gamma(\dot{\mathbf{u}} - \mathbf{v}) + \mathbf{f}_u \quad (2)$$

$$\rho_F\dot{\mathbf{v}} - \eta\nabla^2\mathbf{v} + \nabla P = \Gamma(\dot{\mathbf{u}} - \mathbf{v}) + \mathbf{f}_v \quad (3)$$

$$\nabla \cdot \mathbf{v} = 0, \quad (4)$$

where P is the pressure and \mathbf{f}_u and \mathbf{f}_v are, respectively, the force densities exerted on \mathbf{u} and \mathbf{v} by the embedded beads. The friction coefficient Γ is estimated by considering a uniform displacement of the network relative to the fluid at constant relative velocity \mathbf{v} . The friction force per unit volume, $\Gamma\mathbf{v}$, is equal to the friction force $\eta\xi\mathbf{v}$ on a strand of the network of length equal to the mesh size ξ divided by ξ^3 , the volume per strand. The result is $\Gamma \sim \eta/\xi^2$.

Our goal is to calculate the frequency-dependent displacement compliance $\alpha(\omega)$ relating bead displacement $\mathbf{r}(\omega)$ to the external force $\mathbf{F}(\omega)$ imposed on it:

$$\mathbf{r}(\omega) = \alpha(\omega)\mathbf{F}(\omega), \quad (5)$$

and to determine under which conditions, if any, the GSER, $\alpha(\omega) = 1/(6\pi a G(\omega))$ applies, *i.e.* under what conditions measurements of the displacement of an individual particle provide a direct measure of the complex shear modulus of the two-fluid medium. The complete solution to this problem requires solving Eqs. 2–4 with time derivatives replaced by $-i\omega$, \mathbf{f}_u and \mathbf{f}_v equal to zero, and with boundary conditions that $\mathbf{u}(\omega) = \mathbf{v}/(-i\omega) = \mathbf{r}(\omega)$ at the surface of the sphere. The resulting functions $\mathbf{u}(\mathbf{x}, \omega)$ and $\mathbf{v}(\mathbf{x}, \omega)$ can then be used to calculate the stress at the surface of the bead and by integration the total force $\mathbf{F}_b(\omega)$ exerted on the medium by the bead. Newton's equation for a bead of mass M , $-\omega^2 M \mathbf{u} + \mathbf{F}_b(\omega) = \mathbf{F}(\omega)$ then determines $\alpha(\omega)$. This procedure is laborious at best, and we will apply a slightly less rigorous one. We localize the bead-medium forces \mathbf{f}_α , ($\alpha = u, v$) on the bead by setting $\mathbf{f}_\alpha(\mathbf{k}, \omega) = \mathbf{F}_\alpha(\omega)\Theta(|\mathbf{k}| - k_{\max})$ where $\mathbf{f}_\alpha(\mathbf{k}, \omega)$ is the Fourier transform of $\mathbf{f}_\alpha(\mathbf{x}, t)$, $\mathbf{F}_\alpha(\omega)$ is the integrated force exerted by the bead, $k_{\max} = \pi/2a$, and $\Theta(x)$ is the unit step function. The total force exerted on the bead by the medium is $\mathbf{F}_b(\omega) = \mathbf{F}_u(\omega) + \mathbf{F}_v(\omega)$ and Newton's equation for a bead is the same as above.

Our procedure is to use Eqs. 2–4 to calculate $\mathbf{u}(\mathbf{k}, \omega)$ and $\mathbf{v}(\mathbf{k}, \omega)$ in terms of $\mathbf{f}_u(\mathbf{k}, \omega)$ and $\mathbf{f}_v(\mathbf{k}, \omega)$, and then to calculate by integration over k , the network displacement $\mathbf{r}(\omega)$ and fluid velocity $\mathbf{w}(\omega)$ at the bead in terms of $\mathbf{F}_\alpha(\omega)$. We then require that the bead, the network, and the fluid all move together at the bead, *i.e.* that $\mathbf{r}(\omega)$ be the bead displacement and $\mathbf{w}(\omega) = -i\omega \mathbf{r}(\omega)$ its velocity. This constraint on $\mathbf{r}(\omega)$, $\mathbf{w}(\omega)$ imposes a particular ratio between $\mathbf{F}_u(\omega)$ and $\mathbf{F}_v(\omega)$ that allows us to obtain a linear relation between $\mathbf{r}(\omega)$ and $\mathbf{F}_b(\omega)$. When applied to a sphere in a Newtonian fluid and expanded in powers of $-i\omega$, this procedure reproduces correctly the constant and $\sqrt{-i\omega}$ contribution to $\alpha^{-1}(\omega)/(-i\omega)$ and the $-i\omega$ inertial contribution with a slightly different prefactor. We expect similar accuracy for the current problem. Our result for $\alpha(\omega)$ can be expressed as

$$\alpha^{-1}(\omega) = \frac{6\pi a G(\omega)(1 - X(\omega))}{\left[1 + H\left(\frac{\omega}{\omega_B}\right) \frac{G(\omega)}{2B} + J(\omega)\right]} - \omega^2 M \quad (6)$$

where we have introduced the complex shear modulus of the material: $G(\omega) = \mu - i\omega\eta$ and the cross-over function, H defined by

$$H(x) = 1 - \int_0^1 dz (1 + iz^2/x)^{-1} \quad (7)$$

as well as the frequency scale: $\omega_B = (2\mu + \lambda)/(a^2\Gamma)$. In this result we assume that the mass density of the elastic network is significantly lower than that of the fluid,

$\rho/\rho_F \ll 1$, owing to the open structure of the network. Consequently, in Eq. (6) we have set $\rho = 0$. We have also introduced the functions J and X which we discuss briefly below. A more complete analysis of this result will be published elsewhere [6]. In order for the result given by Eq. (6) to reduce to the GSER we must find that (at least for some frequency range) $H \approx 0$, $J \approx -X$, and $\beta_b(\omega) = (2\rho_b a^2 \omega^2)/9G(\omega) \ll 1$ where ρ_b is the mass density of the bead.

First we consider H . From Eq. (7) we note that $H(x)$ goes to zero as $1/x$ for $x \gg 1$, so for frequencies large compared to ω_B , we can neglect this term. From an examination of the hydrodynamic modes of the system, the physical interpretation of this result is clear. The frequency scale ω_B is the decay time for the overdamped longitudinal compression mode of the system at the length scale of the bead. In this mode the network undergoes a compressional wave while the fluid drains from the denser parts of the network to the more rarefied parts. The H function, therefore, represents a correction to the microrheological measurements due to the excitation of longitudinal degrees of freedom in the system. Whereas in the macrorheological experiment the applied strain is pure shear, in the microrheological experiment the probe particle responds to all the thermally excited modes of the system including the longitudinal compression modes of the elastic network. At frequencies higher than ω_B , however, the network “locks in” with incompressible fluid thereby eliminating the former's longitudinal modes and bringing the microrheological measurement into closer correspondence with standard rheology. The elimination of the so-called free-draining (longitudinal) mode at large ω has been discussed previously [2].

We now consider the function $J(\omega)$. Its form is controlled by two dimensionless parameters: $\beta_F(\omega) = 4\omega^2 \rho_F a^2 / [G(\omega)\pi^2]$ and $\delta = (\xi/a)^2$. The parameter β_F is formed by the square of the ratio of the sphere's radius to the inertial decay length [7] in the medium and measures the importance of fluid inertial effects in the compliance. The second parameter, δ , simply measures the ratio of the network mesh size to the sphere radius. In the limit that both β_F , $\delta \ll 1$ the function $J(\omega)$ reduces to $-X(\omega)$. Since $\rho_F \sim \rho_b$, β_b and β_F are of the same order and both will be small for $\omega < \omega^*$ with $\beta_b(\omega^*) \sim \beta_F(\omega^*) \sim 1$. Our approximate calculation is expected to reproduce the exact result for $\omega < \omega^*$, so our estimate of the region of validity of the GSER should be correct.

In typical experiments [2], the probe sphere is taken to be orders of magnitude larger than the mesh size so we may safely assume that $\delta \ll 1$. For experiments on actin [2] with a sphere size of $1 \mu\text{m}$, β_F remains small up to frequencies on the order of 50kHz. A similar estimation of the lock-in frequency yields $\omega_B \sim 10\text{Hz}$. Thus in typical experiments there remains a significant frequency window, $\omega_B < \omega < \omega^*$, where the response function of the

probe particle to an applied force is well approximated by the GSER. This model calculation reveals the range of validity of the GSER for typical experiments on soft materials; furthermore it presents a quantitative prediction of the form of the compliance in frequency regimes where the GSER does not hold [6].

We now turn to the issue of rheological heterogeneities introduced by the beads themselves. We imagine a medium characterized by a homogeneous frequency-dependent elastic-constant tensor. The introduction of spherical probe particles perturbs the medium in the vicinity of these particles and leads to a spatially inhomogeneous elastic constant tensor $K_{ijkl}(\mathbf{x}, \omega)$. Assuming that the stress-strain relation remains local, that the frequency regime ($\omega_B < \omega < \omega^*$ for our coupled network) is such that the medium can be characterized by a single, frequency-dependent elastic constant tensor, and that inertial terms can be neglected, the equation for the displacement variables is

$$-\partial_j (K_{ijkl}(\mathbf{x}, \omega) \partial_k u_l) = f_i(\mathbf{x}, \omega), \quad (8)$$

where $f_i(\mathbf{x}, \omega)$ is the force density that acts on the surface of the particles. The displacement responses of the collection of particles to forces upon them can be described by a compliance tensor $\alpha_{ij}^{(nm)}$:

$$R_i^n(\omega) = \alpha_{ij}^{(nm)}(\omega) F_j^m(\omega), \quad (9)$$

where R_i^n is the displacement vector of the n^{th} particle and F_j^m the force on the m^{th} particle. We ask which components of the compliance tensor depend on the bead-imposed inhomogeneities of $K_{ijkl}(\mathbf{x}, \omega)$ and which, if any, depend only on the bulk homogeneous part?

To answer this question, it is useful to consider first the simpler but related problem of determining the bulk dielectric constant of a medium by measuring the self and mutual capacitances of metal spheres whose presence perturbs the dielectric constant in their vicinity. If the dielectric constant $\epsilon(\mathbf{x}, \omega)$ remains local and frequencies are such that transverse electric fields can be ignored, then the potential $\phi(\mathbf{x}, \omega)$ satisfies

$$-\nabla \cdot (\epsilon(\mathbf{x}, \omega) \nabla \phi(\mathbf{x}, \omega)) = 4\pi \rho(\mathbf{x}), \quad (10)$$

where $\rho(\mathbf{x})$ is the charge density at \mathbf{x} . It is clear from Eqs. (8) and (10) that there is an analogy between the electrical and rheological problems with the identification: $\phi \longleftrightarrow \mathbf{u}$, $\epsilon \longleftrightarrow K_{ijkl}$, and $\rho \longleftrightarrow \mathbf{f}$. The total charge Q on a metal sphere is the analog of the total force \mathbf{F} on a bead in the viscoelastic medium. The inverse capacitance tensor C_{nm}^{-1} defined by

$$\phi_n = C_{nm}^{-1} Q_m, \quad (11)$$

where ϕ_n is the potential on bead n and Q_m is the total charge on bead m , is the analog of the compliance tensor.

To keep our calculation simple, we consider two conducting spheres of radius a separated by a distance r in a medium of dielectric constant ϵ . Each sphere perturbs the medium locally, producing a spherical region of radius a' with a dielectric constant $\bar{\epsilon}$ as shown in Fig. (1). To leading order in a/r , the inverse self-capacitance is

$$C_{11}^{-1} = \frac{1}{4\pi\epsilon a} \left\{ 1 + \left(\frac{a'}{a} - 1 \right) \left(1 - \frac{\epsilon}{\bar{\epsilon}} \right) \right\}. \quad (12)$$

This result shows that fluctuations of a single bead are sensitive to the local environment around the bead and that, therefore, they do not measure directly the bulk dielectric constant, ϵ . The inverse mutual capacitance,

$$C_{12}^{-1} = \frac{1}{4\pi\epsilon r} \left(1 + \mathcal{O}\left(\frac{a}{r}\right) \right), \quad (13)$$

depends, however, only on the bulk dielectric constant to leading order in a/r . Thus correlated voltage fluctuations $\langle \phi_1(\omega) \phi_2(-\omega) \rangle = 2(T/\omega) \text{Im} C_{12}^{-1}(\omega)$ yield a direct measurement of $\epsilon(\omega)$ provided the beads are far enough apart that C_{12}^{-1} is proportional to $1/r$.

Given the formal analogy between the electric and mechanical problems, it is reasonable to assume that displacement fluctuations of a *single* bead do not provide a direct measure of the bulk rheological properties whereas correlated fluctuations of *two* beads do, provided the beads are far enough apart. Indeed, we will find this to be the case, however, the vectorial nature of the elastic problem leads to some complications.

We begin by considering a single sphere of radius a that perturbs the elastic medium in which it is embedded out to a radius a' . For $r > a'$, the medium is characterized by bulk Lamé coefficients $\mu(\omega)$ and $\lambda(\omega)$. For $r < a'$ the Lamé coefficients are $\bar{\mu}(\omega)$ and $\bar{\lambda}(\omega)$. Elastic displacements $\mathbf{u}_{\text{inner}}$ in the inner ($r < a'$) and $\mathbf{u}_{\text{outer}}$ in the outer ($r > a'$) regions satisfy the equation

$$\mu \nabla^2 \mathbf{u} + \lambda \nabla (\nabla \cdot \mathbf{u}) = 0, \quad (14)$$

where the Lamé constants take their appropriate values in each region. Putting the force applied to the sphere in the \hat{z} direction, the most general solution for \mathbf{u} is

$$\begin{aligned} \mathbf{u} = & \frac{aA}{r} (\nu \hat{r} \cos \theta + \hat{z}) + \frac{a^3 B}{r^3} (3\hat{r} \cos \theta - \hat{z}) + \\ & + C \hat{z} + \frac{Dr^2}{a^2} (\sigma \hat{r} \cos \theta - \hat{z}) \end{aligned} \quad (15)$$

where A, B, C , and D are constants. The constants ν and σ depend only on the local Lamé constants. The solution for the strain field as written in Eq. (15) includes a superposition of a part that decays with distance as $1/r$ and a dipolar term. These first two terms are accompanied by two other solutions: a constant shift and a term growing with distance from the sphere. The later two terms cannot occur in $\mathbf{u}_{\text{outer}}$ as that field must go to zero

at large distances from the sphere. Thus in the bulk solution for the strain we have two undetermined constants (A and B) while the inner solution ($\mathbf{u}_{\text{inner}}$) has four undetermined constants. The application of the boundary conditions at infinity has reduced the problem to finding six constants. Due to the rigidity of the sphere, the displacement is fixed at its surface. This boundary condition contributes two more constraints. The remaining four conditions come from strain field continuity at the interface of the two elastic media ($r = a'$) and the continuity of the two components of the stress tensor at that interface, σ_{rr} and $\sigma_{r\theta}$. The problem is now completely determined.

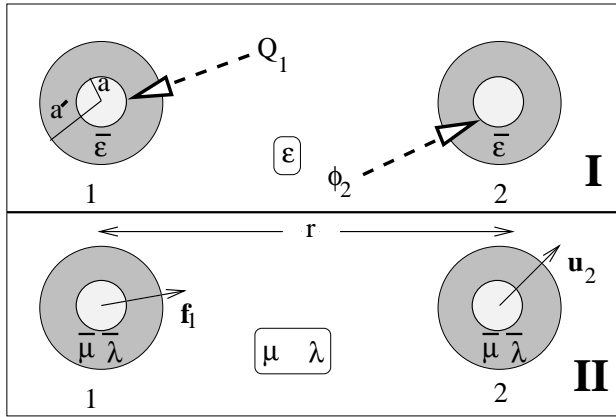


FIG. 1. I. Schematic of a system in which conducting spheres of radius a embedded in a medium of dielectric constant ϵ are surrounded by concentric spheres of radius a' with dielectric constant $\bar{\epsilon}$. II. Similar schematic of rigid spheres embedded in an elastic medium with Lamé coefficients μ , λ surrounded by concentric spheres with Lamé coefficients $\bar{\mu}$, $\bar{\lambda}$.

The complete solution shows that the self-component, α_{ij}^{11} , of the compliance tensor depends in a complex way on the local Lamé coefficients $\bar{\mu}$ and $\bar{\lambda}$. Thus as in the electrical case, fluctuations of a single bead will not yield reliable measurements of bulk rheology unless $a'/a - 1 \ll 1$ or $\bar{\mu}$, $\bar{\lambda}$ do not differ significantly from μ , λ .

To compute the cross component, $\alpha_{ij}^{21}(\omega)$, of the compliance tensor relating displacements of bead 2 to forces on bead 1, we observe that bead 2 will follow the displacement field produced by bead 1 at separations r large compared to a . Thus α_{ij}^{21} is simply the coefficient of F_j^1 in the displacement field of bead 1. At large r , only the first term in Eq. (15) survives. The coefficient A in this term is determined by a global property of the stress field

$$F_z = \oint ds_j \sigma_{jz}, \quad (16)$$

where the integral is over any closed surface surrounding the sphere. Only the $1/r$ part of the displacement field contributes to this integral. From this constraint we can calculate A_{outer} , the coefficient of the first term in Eq. (15) in the outer region ($r > a'$). This coefficient

is linear in F_z . From this, we find that the compliance tensor can be decomposed into parts, α_{\parallel} , parallel to the vector \mathbf{r} separating the two beads and, α_{\perp} , perpendicular to \mathbf{r} : $\alpha_{ij}^{21}(\omega) = \alpha_{\parallel} \hat{r}_i \hat{r}_j + \alpha_{\perp} (\delta_{ij} - \hat{r}_i \hat{r}_j)$ with

$$\alpha_{\parallel} = \frac{1}{4\pi r \mu(\omega)} \quad (17)$$

$$\alpha_{\perp} = \frac{1}{8\pi r \mu(\omega)} \frac{\lambda(\omega) + 3\mu(\omega)}{\lambda(\omega) + 2\mu(\omega)}. \quad (18)$$

Thus fluctuations parallel to the separation vector depend only on the shear modulus, $\mu(\omega) = G(\omega)$, whereas those perpendicular to the line of centers depend on both λ and μ . In the incompressible limit, $\alpha_{\perp}/\alpha_{\parallel} = 1/2$, which is identical to the ratio of the parallel and perpendicular diffusivities of two spheres with (incompressible) hydrodynamic interactions [8], in agreement with recent experimental results on two-point microrheology in a viscous liquid [3]. The experimental determination of this ratio in viscoelastic materials can be used to test for compressibility effects at the frequencies relevant to the experiment.

The combination of single-particle and two-particle position correlations provide data about both the local environment of the probe particle and the bulk material. To test these ideas we suggest that two particle position correlations should be measured at smaller particle separations where $\alpha \approx 1/r$. Correlations should then be sensitive to the particle's local environment.

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